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Allometric scaling of electrical excitation and propagation in the mammalian heart

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Abstract

Variations in body mass impose constraints on the structure and function of mammalian species, including those of the cardiovascular system. Numerous biological processes, including cardiovascular parameters, have been shown to scale with body mass (BM) according to the law of allometric scaling: $Y = a \cdot BM^b$ (Y , biological process; a , normalization constant; b , scaling exponent, which in many instances is a multiple of $1/4$). These parameters include heart and breathing rates, intervals and subintervals of the electrocardiogram (ECG), action potential duration (APD), metabolic rate, and temporal properties of ventricular fibrillation. For instance, the hierarchical branching networks of the vascular system, and of the specialized conduction system in the heart have been proposed to be important determinants of allometric scaling. A global and unifying molecular mechanism of allometric scaling has not been put forth, but changes in gene expression have been proposed to play an important role. Even though it is accepted that differences in body size have cardiovascular effects, the use of scaling in the clinical setting is limited. An increase in the clinical utilization of scaling is thought to lead to improved cardiovascular disease diagnosis and management in patients.

1. Introduction

One of the most evident features of living organisms is their diversity in size. However, the structural and functional effects of change in body mass are at times overlooked. Nature is governed by a set of physical laws, and all organisms live within the limits and constraints set forth by such laws. This concept has been helpful in shedding light on why animal size is important in determining the structural and functional capabilities of living organisms (Schmidt-Nielsen, 1984; Calder, 1984).

Allometric scaling deals with the structural and functional consequences of changes in size or scale among otherwise similar organisms (Schmidt-Nielsen, 1984). Regardless of the remarkable variations in body mass of mammals (from the 5 g shrews to the 30,000 kg whales), fundamental biological processes obey patterns when investigated as a function of size (Schmidt-Nielsen, 1984; Calder, 1984). In this review article we will explore the allometric scaling of the electrical properties of the heart, and the possible clinical implications and applications.

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Biological processes scale with body mass (BM) according to the universal law of allometric scaling $Y = a \cdot BM^b$ where Y is the biological process at hand, a is the proportionality coefficient, BM is the body mass, and b is the scaling exponent, which is often a multiple of $\frac{1}{4}$. Examples of processes that have been demonstrated theoretically and experimentally to obey the law of allometric scaling include metabolic rate, lifespan, growth rates, densities of mitochondria and chloroplasts, aortic radius, and heart rate (HR) (Schmidt-Nielsen, 1984; Calder, 1984; West and Brown, 2005; West et al., 1997; West et al., 1999; West et al., 2002; Kleiber, 1947; Turcotte et al., 1998; Noujaim et al., 2004). As an example, Fig. 1A shows a double logarithmic plot of the HR versus BM in animals ranging in size from the mouse to the whale, where HR scales with body mass approximately according to the equation: $HR = 235 \cdot BM^{-0.25}$. More recently, it was shown that the PR interval, and other intervals and subintervals of the electrocardiogram (ECG), as well as the temporal properties of ventricular fibrillation (VF) scale with BM (Noujaim et al., 2004; Gunther and Morgado, 1997; Noujaim et al., 2007)..

The most extensively studied and thoroughly described scaling law is that of the basal metabolic rate (Kleiber, 1947). It has been proposed that metabolic rate scales as $BM^{3/4}$ (West and Brown, 2005; West et al., 1997; West et al., 1999; West et al., 2002; Turcotte et al., 1998). The scaling of metabolic rate has been shown to span 27 orders of magnitude in mass, and applies to small and large animals, unicellular organisms, and even at the subcellular level, all the way down to mitochondria. However, the idea that metabolic rate is proportional to $BM^{3/4}$ continues to be challenged (White and Seymour, 2003; Kolokotronis et al., 2010). Similarly to basal metabolic rate, other biological processes have been shown to follow quarter-power exponent patterns according to the law of allometry. Thus, a unifying theory has been put forward to explain how these multiple of $\frac{1}{4}$ exponents govern the scaling of biological processes across organisms (West and Brown, 2005; West et al., 1997, 1999, 2002; White and Seymour, 2003).

The universal mechanism postulated to elucidate the ubiquitous $\frac{1}{4}$ power law of allometric scaling relies on the hypothesis that living organisms utilize fractal-like, branching, hierarchical networks to transport nutrients and oxygen and remove waste. Three properties of these networks have been theoretically shown to be necessary to explain the $\frac{1}{4}$ power scaling law. First, the networks must be space-filling. Second, the terminal units of the networks must be invariant in size. And third, the energy expenditure for transport across networks is minimized through natural selection. An example of such a network is the mammalian circulatory system, in which blood flow from the heart is subsequently distributed throughout the body via a hierarchical branching network of vessels starting at the aorta, branching into arteries and arterioles, before reaching the terminal capillary units. Other examples include neural systems, the bronchial tree of the respiratory system, and plant vascular systems (West and Brown, 2005; West et al., 1997, 1999, 2002).

1.1. Scaling of the PR interval and subintervals of the intracardiac electrogram

The PR interval measures the time taken by an electrical impulse generated in the sinoatrial (SA) node to propagate from the atria to ventricles. Mammalian BM from the shrew to the whale changes by more than six orders of magnitude, while the PR interval does not change

by more than 10 fold (Noujaim et al., 2004; Meijler, 1985; Meijler, 1990; Meijler et al., 1992, 2002; Meijler and van der Tweel, 1986; van der Tweel et al., 1999). Fig. 1B shows the difference in the heart sizes of the horse, cat, and mouse. Initially it was thought that the PR interval scaled linearly with heart length, however this did not apply to larger animals (Meijler, 1990; Meijler et al., 2002). It was subsequently proposed that this could be attributed to possible differences in the atrioventricular (AV) conduction system of small and large animals (Meijler, 1985; Meijler, 1990; Meijler et al., 2002; James et al., 1995). Afterwards, it was shown theoretically and experimentally that allometric scaling governed the relation between the PR interval of mammals and body size where $PR \propto BM^{1/4}$ (Noujaim et al., 2004). The premise assumed for this scaling relation was that the specialized conduction system of the heart behaves as a branching network that carries the depolarization from the SA node to the ventricles, with a size invariant terminal unit: the cell (Noujaim et al., 2004; James et al., 1995). Using data from 33 species, ranging in size from the humpback whale to the shrew, it was found that the relationship between the PR interval and BM could be described by the equation: $PR = 53 \cdot BM^{0.24}$, where the exponent **0.24** is very close to the predicted value of **0.25** (Noujaim et al., 2004). Fig. 2A is a double logarithmic plot of PR interval versus BM. To further test the validity of the theoretical and experimental findings, data from five different species (mouse to horse) was used to examine the scaling of the PR subintervals (PA, AH, HV). The logic being that the depolarization originating from the SA node is transported to the ventricles through three separate fractal-like, branching networks, progressing in series (the atrium, the AV node, and the His-Purkinje system). Therefore, each of the subintervals should scale with $BM^{1/4}$, and should be a constant fraction of the PR interval, irrespective of BM. It was found that: $PA = 14 \cdot BM^{0.25}$, $AH = 33.8 \cdot BM^{0.25}$, $HV = 16.6 \cdot BM^{0.25}$, where PA, AV, and HV subintervals constitute about 25%, 50%, and 25%, respectively, of the PR interval across all mammalian species (Noujaim et al., 2004). This is illustrated in the plots of Fig. 2B..

The atrial contraction takes place late in diastole, after passive filling of the ventricles has occurred. An appropriately timed atrial “kick” allows for an increase in the ventricular contraction according to the Frank–Starling Law (Benchimol et al., 1965). Therefore, the contraction of the atria is an important determinant of ventricular performance, and therefore, the length of the PR interval plays a role in the optimal timing of this contraction during the cardiac cycle. Consequently, it is suggested that $PR \propto BM^{1/4}$ in order to ultimately maximize the hemodynamic efficiency of the heart (Noujaim et al., 2004). Moreover, the cardiac output scales proportionally to $BM^{3/4}$ and left ventricular ejection time to $BM^{1/4}$ (Popovic et al., 2005).

1.2. Scaling of ventricular fibrillation

VF is a leading cause of sudden cardiac death. During normal sinus rhythm, the excitation-contraction process results in a synchronous ventricular contraction. This synchronous excitation is essential to the heart's effective functioning as a pump. However, during VF, electrical waves no longer follow the usual paths and synchronous ventricular contraction is compromised (Jalife, 2000).

Immediately upon the onset of VF, the heart rate increases substantially and action potential propagation assumes a vortex-like pattern (Jalife, 2000). The rotation frequencies of the vortices, or rotors, that arise during VF have been found to vary depending on the size of the animal (Noujaim et al., 2007). Fig. 3A illustrates the cycle lengths of the vortices in different species, found to be about 28 ms in mice, 36 ms in guinea pigs, 88 ms in sheep, and 153 ms in humans (Noujaim et al., 2007). The frequencies of these rotors scale with BM according to the laws of allometric scaling (Noujaim et al., 2007) where the frequency of $VF=18.9 \cdot BM^{-1/4}$ and inversely the interbeat interval of $VF=53 \cdot BM^{1/4}$ (Fig. 2B). Additionally, the rotor core size (its perimeter), the functional “obstacle” around which the wavefront of excitation and the wave tail rotate is also proportional to $BM^{1/4}$ (Noujaim et al., 2007). This is in contrast to earlier postulations that the rotor core size was invariant in size (Winfree, 1994)..

The mechanism behind the scaling of VF frequency, interbeat interval, and rotor core size can be explained by differences in the action potential duration (APD) of different species (Noujaim et al., 2007). In order for a small mammal to maintain a much faster heart rate, the electrical excitation-recovery cycle, or APD, must be shorter than in a larger mammal. On the ECG, the QT interval is a good approximation to the duration of the entire excitation-recovery cycle of the ventricles, and it has been found to scale in proportion to $BM^{1/4}$ (Gunther and Morgado, 1997). Based on numerical simulations using the simplified Fitzhugh–Nagumo model of membrane kinetics, it has been postulated that the frequency of rotors is strongly dependent on APD which is in turn dependent on $BM^{1/4}$ (Noujaim et al., 2007). As APD increases proportionally to $BM^{1/4}$, the frequency of VF decreases proportionally to $BM^{-1/4}$ (Noujaim et al., 2007).

The fact that the temporal properties of VF and the rotor core sizes scale with $BM^{1/4}$ suggests that significant similarities in the underlying mechanisms of this fatal arrhythmia exist in most, if not all, mammals (Noujaim et al., 2007; Panfilov, 2006).

1.3. Molecular and cellular mechanisms of action potential duration scaling

The heart mass scales isometrically with BM; i.e., heart mass is a constant fraction of BM, estimated to be about 0.6% (Schmidt-Nielsen, 1984; Calder, 1984). In addition, no significant differences exist in the gross morphology of the heart or cardiac myocytes species' body weights change (James et al., 1995). Furthermore, physiological properties, such as mean arterial pressure and cell size, remain relatively constant across mammalian species (West and Brown, 2005). However, cardiac electrophysiological properties, such as heart rate and ECG intervals (Noujaim et al., 2004), as well as APD (Noujaim et al., 2007; Rosati et al., 2008), scale with BM. The mechanisms that underlie electrophysiological scaling are thought to involve complex changes in the expression of different ion channels and transporters that play integral roles in the electrical excitation and recovery of the heart (Rosati et al., 2008; Rosati and McKinnon, 2009).

Two basic principles have been proposed to explain the evolution of the molecular mechanisms of biological systems, including the heart's electrophysiological properties. Evolutionary differences among species can occur either due to modifications of gene regulation (regulatory evolution) or due to changes in protein structure and function

(structural evolution) (Rosati et al., 2008; Rosati and McKinnon, 2009). The structural and functional properties of the ion channels responsible for APD, action potential morphology, and duration of myocyte contraction remain relatively similar across species. However, their gene regulation and expression varies drastically. It is thought that this variation in gene regulation is responsible for the molecular and cellular mechanisms of scaling (Rosati et al., 2008; Rosati and McKinnon, 2009).

As previously mentioned, the APD scales over a wide range of body weights (Noujaim et al., 2007; Rosati et al., 2008), but at the cellular level, substantial differences exist in the action potential waveform. In species smaller than guinea pigs, repolarization is heavily dependent on the transient outward potassium current (I_{to}), and to some extent, the inward rectifier potassium current (I_{K1}). In guinea pigs and larger species, the slow delayed rectifier potassium current (I_{Ks}), the rapid delayed rectifier potassium current (I_{Kr}), and I_{K1} control repolarization (Rosati et al., 2008). The presence of the large and rapid I_{to} in smaller animals prevents the formation of a plateau phase, and consequently the shape of the action potential is “triangular”, whereas larger animals do exhibit an action potential plateau as well as a “spike and dome” appearance.

Action potential shape differences between small and large animals have been proposed to be in part due to changes in gene expression of the ion channels that mediate the I_{to} and I_{Kur} . The expression of the primary molecular component of the I_{to} channel, Kv4.2, and an essential component of the I_{Kur} channel, Kv2.1, is greater in smaller species and is uniformly low in larger species (Rosati et al., 2008; Xu et al., 1999). Furthermore, among species, distinct differences in the proximal promoter regions of the Kv4.2 and Kv2.1 genes were noted, consistent with the differences in mRNA expression (Rosati et al., 2008). This detail suggests that these differences in expression are mediated by *cis*-regulatory elements, as opposed to changes in transcription factor networks. Differences in the expression of voltage-gated potassium channels that carry I_{Ks} and I_{Kr} also have an effect on the action potential (Rosati et al., 2008). These findings suggest that modifications in expression of these genes contribute to the scaling of the APD.

Other channels, including calcium channels and calcium handling proteins have been shown to undergo changes in their patterns of expression as body size changes. For instance, the peak L-type calcium current is larger in the mouse compared to the guinea pig and the dog (Rosati et al., 2008). On the other hand, because heart rate increases and APD abbreviates as BM decreases (Noujaim et al., 2004; Noujaim et al., 2007; Rosati et al., 2008), it is likely that the calcium transient duration also decreases to accommodate a faster heart rate.

There are two mechanisms responsible for clearing calcium from the cytosol following an action potential. The first uses the Ca^{2+} -ATPase pump to sequester calcium in the sarcoplasmic reticulum, while the second mechanism utilizes the Na^{+}/Ca^{2+} exchanger to extrude calcium out of the myocyte (Rosati et al., 2008). Although the expression of the Na^{+}/Ca^{2+} exchanger remains relatively constant among species, expression of the Ca^{2+} -ATPase pump increases significantly with decreasing BM (Rosati et al., 2008). mRNA levels encoding the Ca^{2+} -ATPase pump increase as BM decreases, suggesting that this change in expression is mediated at the level of transcription (Rosati et al., 2008). It has also been

shown that transcription of the alpha subunit of the sodium channel (Nav1.5) is increased in smaller species. Since smaller mammals also exhibit increased expression of the large and rapid I_{to} , it is postulated that the increase in sodium channels is a compensatory mechanism to help maintain the peak height of the action potential (Rosati et al., 2008).

1.4. Clinical implications

Accurate measurement of heart dimensions and function is essential in diagnosing cardiovascular disease. Yet, criteria set forth to distinguish a disease state from a normal variant are often unclear, and overlap does exist between physiology and pathophysiology over variable ranges. Such overlap can be attributed, in part, to differences in body size. Even though the scaling of numerous cardiovascular parameters to BM is relatively accepted, it is utilized inconsistently in the clinical setting. For instance, in the pediatric clinic, measurements are scaled to body size since significant size variations exist in the pediatric population. In the adult population, however, such variations are usually not taken into account (Dewey et al., 2008). The National Health and Nutrition Examination Survey (NHANES) proposed that the possible effects of body size should be considered (Ogden et al., 2004). Disregarding these differences and their possible effects on cardiovascular parameters could potentially affect the diagnosis and management of various cardiovascular diseases (Dewey et al., 2008).

In the adult clinical practice, the number of cardiovascular parameters that are scaled is limited. Furthermore, the scaling is done ratiometrically, where the cardiovascular variable is simply divided by a measure of body size. Ratiometric scaling assumes a linear relationship between the cardiovascular “variable” and the body size (Dewey et al., 2008). However, as has been discussed thus far, many of the cardiovascular parameters scale with body size in a more complex allometric manner. Another factor to consider in assessing the accuracy of clinical scaling is the body size variable that is used. For instance, the cardiovascular system's inherent function is to distribute oxygen to the tissues. The variables most often used are body surface area (BSA) and BM (Dewey et al., 2008). However, the respective contribution of tissue types (e.g., tissue with high metabolic demand, such as muscle, versus tissue with minimal metabolic demand, such as extracellular fluid or fat) to these body size variables can vary drastically from patient to patient. For instance, extracellular volume contributes significantly more to the BSA and BM of patients with congestive heart failure as compared to healthy controls. Furthermore, adipose tissue constitutes a much greater proportion of BSA and BM in obese individuals as compared to elite athletes. These differences call for utilization of body size variables that represent the most metabolically active tissue, such as fat free mass or lean body mass (Dewey et al., 2008). Consequently, further studies should be focused on utilizing and optimizing scaling to aid in the diagnosis and management of cardiovascular disease.

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Fig. 1.

A- Double logarithmic plot of heart rate (HR) versus body mass (BM) in 33 species ranging in size from mouse to whale. The best fit line in red is $y=5.5-0.22x$; $R=-0.96$, where $\text{HR} \sim 235 \cdot \text{BM}^{-0.25}$. Green lines are the 95% confidence limits. **B-** Variation in the heart size across four orders of magnitude in BM (horse, cat, and mouse). Modified with permission from (Noujaim et al., 2004).

Fig. 2.

A- Double logarithmic plot of PR interval versus BM in 33 species ranging in size from mouse, spanning six orders of magnitude in BM. The best fit line in red is $y=2.4+0.24x$; $R=0.92$, where $\text{PR} \sim 53 \cdot \text{BM}^{0.25}$. Green lines are the 95% confidence limits. B- Double logarithmic plots of PA, AH, and HV subintervals versus body mass (rat to horse). The best fits (solid black lines) are $y=2.6+0.25x$ for PA, $y=3.5+0.22x$ for AH, and $y=2.8+0.22x$ for HV, where $\text{PA} \sim 14 \cdot \text{BM}^{0.25}$, $\text{AH} \sim 33.8 \cdot \text{BM}^{0.25}$, and $\text{HV} \sim 16.6 \cdot \text{BM}^{0.25}$. Dotted and broken lines are 95% confidence and prediction limits, respectively. Modified with permission from (Noujaim et al., 2004).

Fig. 3.

A- Four action-potential-phase snapshots depicting a rotation of rotors during ventricular fibrillation in mouse, guinea pig, sheep, and human hearts. Vortex-like reentry is apparent in all hearts. The white circular arrows show the location of the center and the direction of rotation. Numbers represent time of one cycle in milliseconds. B- Double logarithmic plot of VF frequency vs. BM covering 11 species, from mouse to horse. Best fit (solid line) is $y=2.94-0.23x$; $R=-0.93$. VF Frequency $\sim 18.9 \cdot \text{BM}^{-0.25}$, and VF cycle length $\sim 53 \cdot \text{BM}^{0.25}$. Short dashed lines and long dashed lines indicate 95% confidence and prediction limits, respectively.

Modified with permission from (Noujaim et al., 2007).